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(54) Use of corticotropin releasing factor (CRF) antagonists to prevent sudden death

(57) A method of preventing sudden death which comprises administering to a mammal, including a human, a therapeutically effective amount of a corticotropin releasing factor antagonist.

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Description

BACKGROUND OF THE INVENTION

[0001] This invention relates to methods for reducing the incidence of sudden death in certain patients by administering thereto a pharmaceutically effective amount of a corticotropin releasing factor (CRF) antagonist. It is currently believed that CRF antagonists reduce the incidence of sudden death in patients by improving their QT dispersion and heart rate variability.

[0002] Sudden unexpected death occurs in about 50% of patients suffering from mild heart failure and in 25% of patients experiencing severe heart failure (Barr et al., *Lancet*, 343(8893):327-29 (1994)). Regional variation in ventricular repolarization, which represents an electrophysiological substrate for arrhythmias, can be detected by inter-lead variability of the QT interval (dispersion). Increased QT interval dispersion has been shown in patients who develop ventricular tachyarrhythmias after an acute myocardial infarction, long QT syndrome, chronic heart failure, and hypertrophic cardiomyopathy (see, e.g., Potratz et al., *Eur. Heart J.*, 14:254 (1993); Day et al., *Br. Heart J.*, 63:342-44 (1990); and Buja et al., *Am. J. Cardiol.*, 72:973-976 (1993)).

[0003] The compounds of formulas I and II as described herein, their pharmaceutically acceptable salts, and methods of preparing such compounds and salts are disclosed in European patent application number EP 0773023 A1, and in more detail in PCT international patent application numbers PCT/IB95/00373 (published as WO 95/34563), PCT/IB95/00439 (published as WO 95/33750), PCT/US93/11333 (published as WO 94/13677), and PCT/US93/10715 (published as WO 94/13676). These European and PCT international patent applications, referred to above, are incorporated herein by reference in their entirety.

[0004] The foregoing PCT international patent applications refer to the use of the compounds of formulas I and II in the treatment of illnesses induced or facilitated by CRF and in the treatment of anxiety, depression, fatigue syndrome, gastrointestinal diseases, headache, pain, cancer, immune dysfunction, hemorrhagic stress, drug addiction, drug and alcohol withdrawal symptoms, fertility problems, stress-induced psychotic episodes, neurodegenerative diseases such as Alzheimer's disease, irritable bowel syndrome including Crohn's disease, spastic colon, and irritable colon, eating disorders such as anorexia nervosa, inflammatory disorders such as arthritis, asthma, and allergies.

[0005] Other CRF antagonists that can be used to treat the disorders recited in the method of this invention are referred to in PCT international patent application numbers PCT/IB95/00318 (published as WO 95/33727), PCT/IB97/00918 (published as WO 98/05661), PCT/IB97/00904 (published as WO 98/08846), and PCT/IB97/00922 (published as WO 98/08847), PCT/EP98/02267 (published as WO 98/47874), PCT/EP98/02268 (published as WO 98/47903), PCT/US98/09861 (published as WO 98/51312), PCT/US98/13840 (published as WO 99/01439), PCT/US98/13913 (published as WO 99/01454), as well as in United States Patents 5,063,245, 5,109,111, 5,132,111, 5,245,009, 5,464,847, 5,493,006, 5,510,458, 5,605,642, 5,644,057, 5,663,292, 5,668,145, 5,705,646, and 5,712,303. All of the above-cited PCT international patent applications and United States Patents are incorporated herein by reference in their entirety.

[0006] The importance of CRF antagonists is set out in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference in its entirety. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., *Pharm. Rev.*, 43:425-73 (1991), also incorporated herein by reference in its entirety.

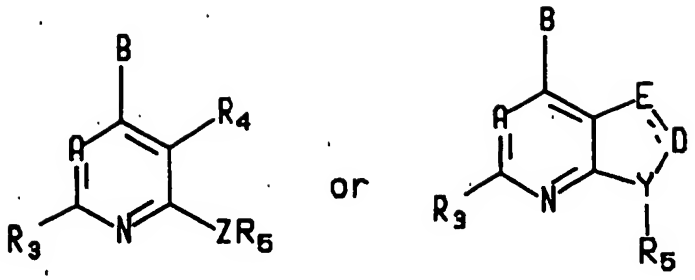
[0007] PCT international patent application PCT/US98/07831 (published as WO 98/47899) discloses the usefulness of substituted pyrrolopyridines in the treatment of inflammatory diseases. The disclosed compounds inhibit the production of certain inflammatory cytokines, namely TNF-α and IL-1β. One of the listed cytokine-related inflammatory diseases is congestive heart failure. However, no mention is made of QT dispersion or heart rate variability.

SUMMARY OF THE INVENTION

[0008] The present invention relates to a method of preventing sudden death in an animal comprising administering to said animal, preferably a human, a therapeutically effective amount of a corticotropin releasing factor antagonist.

[0009] The method of the present invention is most useful in preventing sudden death in specific patients, particularly those suffering from cardiovascular or heart related diseases such as hypertension, tachycardia, congestive heart failure, and the like, as well as other diseases such as stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, colonic hypersensitivity associated with psychopathological disturbance and stress, and the like. The method of the present invention is also useful in preventing sudden death in diabetic patients, as well as in patients suffering from many neurological disorders such as brain damage, Guillain-Barre syndrome, sudden infant death syndrome, congenital hypoventilation syndrome, uremic neuropathy, and the like.

[0010] In a preferred embodiment, the present invention is practiced using a compound of Formula I or II:



I or II

or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;
A is $-CR_7$ or N;
B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;
D is

N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$;
$-CR_{10}$ when a double bond connects E and D and E is N; or
$-CR_8R_9$, $-CHR_{10}$, -C=O, -C=S, -C=NH, or $-C=NCH_3$ when a single bond connects E and D;

E is $-CR_4$ or N when a double bond connects E and D, and E is $-CR_4R_6$ or $-NR_6$ when a single bond connects E and D;
Y is N or -CH;
Z is NH, O, S, $-N(C_1-C_2$ alkyl), or $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl, or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;
R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with up to two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, $-O-CO-(C_1-C_4$ alkyl), $-O-CO-NH(C_1-C_4$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl$(C_1-C_4$ alkyl), $-S(C_1-C_4$ alkyl), $-N(C_1-C_4$alkyl)$CO(C_1-C_4$ alkyl), $-NHCO(C_1-C_4$ alkyl), $-CO_2(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $-CON(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $(C_1-C_4$ alkyl)sulfinyl, $(C_1-C_4$ alkyl)sulfonyl, and $(C_1-C_4$ alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;
R_2 is C_1-C_6 alkyl, heteroaryl, aryl, heteroaryl $(C_1-C_4$ alkyl), or aryl $(C_1-C_4$ alkyl), wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl and naphthyl, and said heteroaryl and the heteroaryl moiety of said (heteroaryl)C_1-C_4 alkyl is selected from the group consisting of thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or $(C_3-C_8$ cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said $(C_3-C_8$ cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by up to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, $-O-CO-(C_1-C_4$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-CO_2(C_1-C_4$ alkyl), $(C_1-C_4$ alkyl)sulfanyl, $(C_1-C_4$ alkyl)sulfinyl, and $(C_1-C_4$ alkyl)sulfonyl, and wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;
or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated or partially saturated 5- to 8-membered ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by a heteroatom selected from O, S, and N;
R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-CH_2OH$, $-CH_2OCH_3$, $-O(C_1-C_4$ alkyl), $(C_1-C_4$ alkyl)sulfanyl, $(C_1-C_4$ alkyl)sulfonyl, or $(C_1-C_4$ alkyl)sulfinyl, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino,

C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -NHCOCH$_3$, fluoro, chloro, and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2CF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N$(CH_3)_2$, -NHCOCH$_3$, -NHCONHCH$_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano, and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or a 3- to 8-membered cycloalkyl ring or a 9- to 12-membered bicycloalkyl ring system, wherein said cycloalkyl ring and said bicycloalkyl ring system optionally contain one or two of O, S, or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl, or benzyl, wherein each of the above R_5 groups is optionally substituted by up to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy, and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino, and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy, or fluoro group;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3, or -$CH_2OCH_2CH_3$;

R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy;
or R_8 and R_9 together form an oxo (=O) group;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), cyano, carboxy, amido, or -SO_n(C_1-C_4 alkyl) wherein n is 0, 1, or 2, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano, or nitro; and

R_{11} is hydrogen, hydroxy, fluoro, or methoxy.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Improvement in QT dispersion by CRF antagonists by normalizing the parasympathetic and sympathetic electrical influence on the heart will result in decreased incidence of fatal ventricular arrhythmias resulting in reduced mortality. Similarly, CRF antagonists will reduce mortality by the improvement of heart rate variability through the same mechanism. Heart rate variability is the amount of fluctuations around the mean heart rate, and can be used as a correlate of the cardiorespiratory control system. Low heart rate variability, i.e., predominance of either the parasympathetic or sympathetic system, is associated with sudden cardiac death in diabetic, heart failure, and post-infarction patients and in many neurological disorders such as brain damage, Guillain-Barre syndrome, sudden infant death syndrome, congenital hypoventilation syndrome, uremic neuropathy, and the like. (see, e.g., Malpas et al., *Diabetes*, 39:1177-1181 (1990); Woo et al., *J. Am. Coll. Cardiol.*, 23:565-569 (1994); Bigger et al., *Circulation*, 85:164-171 (1992); and van Ravenswaaij-Arts et al., *Annals of Internal Medicine*, 118:436-447 (1993)).

[0012] CRF antagonists decrease the incidence of sudden death due to a centrally mediated imbalance in the neural outflow to the heart and respiratory system in a number of disorders. Patients at risk can be easily and inexpensively monitored by means of electrocardiogram QT dispersion and heart rate variability to determine if they would benefit from such therapy.

[0013] In addition to disease states, certain drugs administered to a patient to alleviate other symptoms may cause or result in QT dispersion and/or heart rate variability. Examples of such drugs include phenothiazine and atypical antipsychotics (e.g., chlorpromazine, respiradone), class 1A and class III antiarrhythmics (e.g., quinidine and sotolol), anesthetic agents (e.g., enflurane, isoflurane), and the like. In such a case, it may also be beneficial to administer a CRF antagonist in order to normalize the parasympathetic and sympathetic electrical influence on the heart and improve the QT dispersion and heart rate variability of the patient.

[0014] While the use of CRF antagonists alone will decrease the incidence of sudden death in certain patients, it may be preferable to combine the CRF antagonist with another drug. For example, other drugs that are also able to balance the neural outflow to heart and/or respiratory system may improve the efficacy of the CRF antagonist in a syner-

gistic manner.

[0015] Preferred for use in the methods of the present invention are the compounds of formulas I and II, and their pharmaceutically acceptable salts, which are readily prepared. The compounds of formula II wherein A, D, and Y are N, a double bond connects E and D, and E is $-CR_4$, are prepared by one or more of the synthetic methods described in PCT publication WO 94/13677, referred to above. The compounds of formula II wherein A and Y are N, a double bond connects E and D, E is $-CR_4$, and D is $-CR_{10}$, are prepared by one or more of the synthetic methods described in PCT publication WO 94/13676, referred to above. The compounds of formula II wherein A is $-CR_7$, a double bond connects E and D, E is $-CR_4$, D is N or $-CR_{10}$, and Y is N, are prepared by one or more of the synthetic methods described in PCT publication WO 95/34563, referred to above. The remaining compounds of formula II and the compounds of formula I are prepared by one or more of the synthetic methods described in PCT publication WO 95/33750, referred to above. Additional information useful in preparing certain of the described compounds is provided in PCT/IB95/00437 (published as WO 96/39388), which described the production of certain intermediates.

[0016] Pharmaceutically acceptable salts of the compounds of formulas I and II include salts of acidic or basic groups. For example, pharmaceutically acceptable salts include sodium, calcium, and potassium salts of acidic groups, such as when the R_{10} substituent is carboxy. Such salts are generally prepared by combining a compound of formula I or II with one molar equivalent of NaOH or KOH in a suitable solvent, pharmaceutically acceptable acid addition salts of basic groups, such as amino groups, are formed by reacting the base form of a compound of formula I or II with an appropriate acid. Pharmaceutically acceptable salts of basic groups include hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate), and p-toluenesulfonate (tosylate) salts. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), at least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate, or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration or addition of a non-solvent.

[0017] Whenever reference is made herein to 3- to 8-membered cycloalkyl rings or 9- to 12-membered bicycloalkyl ring systems, each of which may optionally contain one or two of O, S, or -N-G, it is understood that the oxygen and sulfur atoms are not adjacent to each other in the cycloalkyl ring or bicycloalkyl ring system. When the cycloalkyl ring is three membered, it may only contain one of O, S, or -N-G. An example of a six-membered cycloalkyl ring having O and NH is morpholinyl.

[0018] Whenever R_2 or R_5 is a heterocyclic group, the group is attached through a carbon atom.

[0019] Formulas I and II, referred to above, are intended to include all stereoisomers (e.g., all geometric and optical isomers) as well as racemates of all compounds within the depicted genus.

[0020] In the methods of the invention, the compounds of formulas I and II, and their pharmaceutically acceptable salts, can be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions, and various organic solvents. The pharmaceutical compositions formed by combining the active compounds and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions, and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients, and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate, and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid, and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin, and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate, and talc are often useful for tabletting purposes. Solid compositions of a similar type can also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, and combinations thereof. Oral administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, another route of administration such as suppositories, parenteral, or topical administration will be appropriate.

[0021] For parenteral administration, solutions of the active compound in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution can be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

[0022] For purposes of transdermal (e.g., topical) administration, dilute, sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are employed.

[0023] Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in the art. For example, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., 15th Edition (1975).

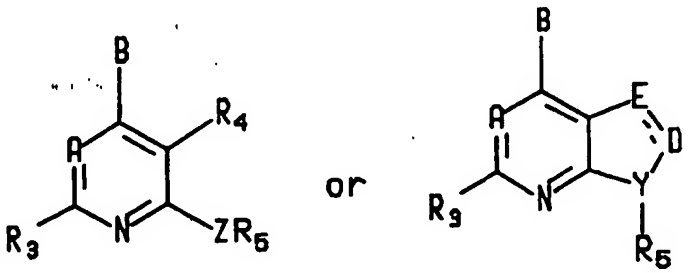
[0024] In the methods of the invention, the effective dosage for the compounds of formulas I and II, and their pharmaceutically acceptable salts, depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. In general, the daily dosage will preferably be about 0.1 mg/kg to about 50 mg/kg of the body weight of the patient to be treated. More preferably, the daily dosage will be about 1.0 mg/kg to about 20 mg/kg of body weight. The daily dosage may be given in a single dose or in divided doses.

[0025] The methods of screening the compounds of formulas I and II, and their pharmaceutically acceptable salts, for CRF antagonist activity are as described in Wynn et al., *Endocrinology*, 116:1653-1659 (1985) and Grigoriadis et al., *Peptides*, 10:179-188 (1989), These methods determine the binding affinity of a test compound for a CRF receptor, which is highly related to its expected activity as a CRF antagonist. The binding affinities for the active compounds, expressed as IC_{50} values, generally range from about 0.2 nanomolar to about 10 micromolar.

Claims

1. A method of preventing sudden death in an animal comprising administering to said animal a therapeutically effective amount of a corticotropin releasing factor antagonist.

2. The method of claim 1, wherein said corticotropin releasing factor antagonist is a compound of Formula I or II:



I or II

or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;
A is $-CR_7$ or N;
B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}\ R_1\ R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;
D is

N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$;
$-CR_{10}$ when a double bond connects E and D and E is N; or
$-CR_8R_9$, $-CHR_{10}$, -C=O, -C=S, -C=NH, or $-C=NCH_3$ when a single bond connects E and D;

E is $-CR_4$ or N when a double bond connects E and D, and E is $-CR_4R_6$ or $-NR_6$ when a single bond connects E and D;
Y is N or -CH;
Z is NH, O, S, $-N(C_1-C_2$ alkyl), or $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl, or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;
R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with up to two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, $-O-CO-(C_1-C_4$ alkyl), $-O-CO-NH(C_1-C_4$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl)$(C_1-C_4$ alkyl), $-S(C_1-C_4$ alkyl), $-N(C_1-C_4$alkyl)$CO(C_1-C_4$ alkyl), $-NHCO(C_1-C_4$ alkyl), $-CO_2(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $-CON(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $(C_1-C_4$ alkyl)sulfinyl, $(C_1-C_4$ alkyl)sulfonyl, and $(C_1-C_4$ alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;

R_2 is C_1-C_6 alkyl, heteroaryl, aryl, heteroaryl (C_1-C_4 alkyl), or aryl (C_1-C_4 alkyl), wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl and naphthyl, and said heteroaryl and the heteroaryl moiety of said (heteroaryl)C_1-C_4 alkyl is selected from the group consisting of thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by -NR_{14} wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by up to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said -NR_1R_2 and said -$CR_1R_2R_{11}$ are taken together to form a saturated or partially saturated 5- to 8-membered ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by a heteroatom selected from O, S, and N;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CH_2OH, -CH_2OCH_3, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfonyl, or (C_1-C_4 alkyl)sulfinyl, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -$NHCOCH_3$, fluoro, chloro, and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2CF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -$NHCOCH_3$, -$NHCONHCH_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alky)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said alkyl, C_1-C_6 alkoxy, and C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano, and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or a 3- to 8-membered cycloalkyl ring or a 9- to 12-membered bicycloalkyl ring system, wherein said cycloalkyl ring and said bicycloalkyl ring system optionally contain one or two of O, S, or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl, or benzyl, wherein each of the above R_5 groups is optionally substituted by up to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy, and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino, and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy, or fluoro group;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3, or -$CH_2OCH_2CH_3$;

R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy;

or R_8 and R_9 together form an oxo (=O) group;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), cyano, carboxy, amido, or -SO_n(C_1-C_4 alkyl) wherein n is 0, 1, or 2, wherein said C_1-C_6 alkyl and C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano, or nitro; and

R_{11} is hydrogen, hydroxy, fluoro, or methoxy.

3. The method of claim 2 wherein B is -NR_1R_2, -$NHCHR_1R_2$, -$CR_1R_2R_{11}$, -$SCHR_1R_2$, or -$OCHR_1R_2$; R_1 is C_1-C_6 alkyl optionally substituted with a single hydroxy, fluoro, or C_1-C_2 alkoxy group and optionally containing one carbon-carbon double or triple bond; R_2 is benzyl or C_1-C_6 alkyl optionally containing one carbon-carbon double or triple bond,

wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl are optionally substituted with fluoro, C_1-C_2 alkyl, or C_1-C_2 alkoxy; and R_{11} is hydrogen or fluoro.

4. The method of claim 2 wherein R_2 is (aryl)C_1-C_4 alkyl or (heteroaryl)C_1-C_4 alkyl in which said aryl moiety is phenyl, furanyl, or benzofuranyl, and said heteroaryl moiety is thienyl, benzothienyl, thiazolyl, pyridyl, or benzothiazolyl.

5. The method of claim 2 wherein B is NR_1R_2 or CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring optionally having sulfur, oxygen, or, where B is NR_1R_2, one more nitrogen in said ring.

6. The method of claim 2 wherein B is -NHCHR$_1$R$_2$ or -OCHR$_1$R$_2$, wherein the CHR$_1$R$_2$ moiety is a 5- or 6-membered ring optionally containing one oxygen or sulfur.

7. The method of claim 2 wherein R_3 is methyl, chloro, or methoxy; R_4 is methyl, -CH_2OH, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, -CO_2CH_3, -CH_2OCH_3, -CH_2Cl, -CH_2F, amino, or nitro; R_6 is hydrogen, methylsulfinyl, methylsulfanyl, methylsulfonyl, or ethyl; and R_5 is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by one substituent independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_3 hydroxyalkyl, -CO_2(C_1-C_2 alkyl), C_1-C_2 alkylamino, -CO(C_1-C_4 alkyl), and C_1-C_6 alkyl, wherein said C_1-C_6 alkyl and said C_1-C_4 alkyl are optionally substituted by a single hydroxy or fluoro group and optionally contain one carbon-carbon double or triple bond.

8. The method of claim 2 wherein the compound of formula I or II is selected from the group consisting of:

4-(1-ethyl-propoxy)-2,5-dimethy-6-(2,4,6-trimethyl-benzyl)-pyrimidine;
2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl pyridine;
2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl pyridine;
3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;
2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-methoxymethol-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;
[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine;
butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;
butyl-[2-(4-chloro-2 ,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
*N*4-(1-ethyl-propyl)-6-methyl-3-nitro-*N*2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;
*N*4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
*N*4-(1-ethyl-propyl)-6-methyl-*N*2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-(1-ethyl-propyl)-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N-(1-ethyl-propyl)-2-methyl-5-nitro-*N*-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-*N*-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;
*N*4-(1-ethyl-propyl)-6,*N*3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
*N*4-(1-ethyl-propyl)-6,*N*3,*N*3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
6-(1-ethyl-propoxy)-2-methyl-*N*4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine; and
6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one.

9. The method of claim 2 wherein said compound is selected from the group consisting of:

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
3,6-dimethyl-4-(tetrahydrofuran-3-yloxy)-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethyiphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;
3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
4-(1 ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;
2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine]-butan-1-ol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo-[3,4-d]pyrimidin-4-yl]-(1-methylpropyl)amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine;
[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;
2-[7-(2-bromo-4,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol; and
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

10. The method of claim 1 wherein the risk of sudden death is related to the presence of a disease state in said animal, wherein said disease state is heart disease, hypertension, tachycardia, congestive heart failure, stroke, osteoporo-

sis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, colonic hypersensitivity associated with psychopathological disturbance and stress, diabetes, neurological disorders, brain damage, Guillain-Barre syndrome, sudden infant death syndrome, congenital hypoventilation syndrome, or uremic neuropathy.

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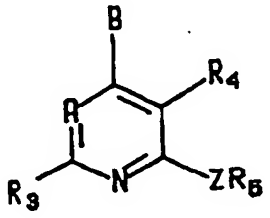
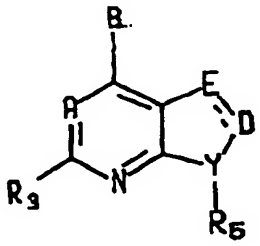
(54) Use of corticotropin releasing factor (CRF) antagonists to prevent sudden death

(57) A method of preventing sudden death which comprises administering to a mammal, including a human, a therapeutically effective amount of a corticotropin releasing factor antagonist. More specifically, said corticotropin releasing factor antagonist is a compound of Formula I or II:



I

or



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Application Number EP 00 30 2253

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X,D	WO 98 08847 A (PFIZER ;CHEN YUHPYNG LIANG (US)) 5 March 1998 (1998-03-05) * page 43 - page 46; examples 10-20 * * page 1, line 33 - page 2, line 17 * * claims 1-13,22,23 * ---	1-10	A61K31/437 A61K31/44 A61K31/455 A61K31/506 A61K31/519
X,D	EP 0 773 023 A (PFIZER) 14 May 1997 (1997-05-14) Formulae I and II All examples * page 2, line 5 - line 10 * * page 2, line 38 - page 5, line 49 * ---	1-10	
X	NAKAMORI T ET AL: "EFFECT OF A CENTRAL CRF ANTAGONIST ON CARDIOVASCULAR AND THERMOREGULATORY RESPONSES INDUCED BY STRESS OR IL-1BETA" AMERICAN JOURNAL OF PHYSIOLOGY, AMERICAN PHYSIOLOGICAL SOCIETY, BETHESDA, MD, US, vol. 265, October 1993 (1993-10), pages R834-R839, XP0010I8317 ISSN: 0002-9513 * abstract * * page R837, line 19 - line 22 * --- -/--	1,10	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 November 2002	Strack, E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
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Although claims 1-10 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
8,9

Claim(s) searched incompletely:
1-7,10

Reason for the limitation of the search:

Present claims 1,10 relate to a compound defined (inter alia) by reference to a desirable characteristic or property, namely "corticotropin releasing factor antagonist".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole scope of the claims is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the compound by reference to its pharmacological profile. This lack of clarity in the present case is such as to render a meaningful search over the whole scope of the claims impossible.

In addition to the preceding objection, present claims 2-7 relate to a rather elevated number of possible compounds, although support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found for only a very limited number of compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, the claims relate to pathological conditions referred to as "heart disease" as the characterising feature. Based upon information readily available, the skilled person would not be aware of all the pathologies possibly involving heart disease. The use of this expression in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search for the first invention has been restricted to those parts of the claims which appear to be clear, supported and disclosed, namely the use of the compounds specifically mentioned in claims 8 and 9 in relation to sudden death resulting from tachycardia and congestive heart failure.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 30 2253

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y,D	WO 95 33750 A (PFIZER ;CHEN YUHPYNG L (US)) 14 December 1995 (1995-12-14) * claims 1-22 * Formulae I, II, III All examples ---	1-10	
Y,D	WO 95 34563 A (PFIZER ;CHEN YUHPYNG L (US)) 21 December 1995 (1995-12-21) * claims 1-14 * Formula I ---	1-10	
Y	DATABASE MEDLINE [Online] 15 December 1996 (1996-12-15) DOVAL H C ET AL: "Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators." Database accession no. NLM8989129 XP002220306 * abstract * & CIRCULATION. UNITED STATES 15 DEC 1996, vol. 94, no. 12, 15 December 1996 (1996-12-15), pages 3198-3203, ISSN: 0009-7322 --- -/--	1-10	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 30 2253

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	DATABASE MEDLINE [Online] December 1990 (1990-12) ROULEAU J ET AL: "Predictors of survival and sudden death in patients with stable severe congestive heart failure due to ischemic and nonischemic causes: a prospective long term study of 200 patients." Database accession no. NLM2272001 XP002220307 * abstract * & THE CANADIAN JOURNAL OF CARDIOLOGY. CANADA DEC 1990, vol. 6, no. 10, December 1990 (1990-12), pages 453-460, ISSN: 0828-282X -----	1-10	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 30 2253

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from heart disease/tachycardia/congestive heart failure.

2. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from hypertension.

3. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from stroke/neurological disorders/brain damage/Guillain-Barre syndrome.

4. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from osteoporosis.

5. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from premature birth.

6. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from psychological dwarfism.

7. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from stress-induced fever.

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 30 2253

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

8. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from ulcer.

9. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from diarrhea.

10. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from post-operative ileus.

11. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from colonic hypersensitivity.

12. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from diabetes.

13. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from sudden infant death syndrome.

14. Claims: 1-10 (partially)

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from congenital hypoventilation syndrome.

15. Claims: 1-10 (partially)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 30 2253

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Use of a compound falling under formulae I or II in a pharmaceutical composition for preventing sudden death resulting from uraemic neuropathy.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 30 2253

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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19-11-2002

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82